2010

Solid Supported Synthesis of Secondary Amines via Staudinger and microwave aza-Wittig Reactions

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BUTLER UNIVERSITY HONORS PROGRAM

Honors Thesis Certification

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Thesis title Solid Supported Synthesis of Secondary Amines via Staudinger and microwave aza-Wittig Reactions

Intended date of commencement May 8, 2010

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For Honors Program use:

Level of Honors conferred: University Magna Cum Laude
Departmental

Acknowledgements

First and foremost I would like thank Dr. Paul Morgan for giving me the opportunity to conduct research alongside him for the past few years. I would also like to add a big thank you for all of his guidance and support as my thesis advisor. I am extremely grateful for the time and effort he spent teaching me all of the elements of research and thesis writing. I want to thank the Butler University Chemistry Department for providing students with the means to carry out research projects, and those who provide funding for such research. I would also like to thank Dr. Wilson for allowing me to use her research lab and Dr. Esteb for all of his advice during the thesis writing process.

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Glossary of Terms

^{1}H NMR: Proton Nuclear Magnetic Resonance

IR: Infrared

GC-MS: Gas Chromatography Mass Spectrometry

THF: Tetrahydrofuran

TLC: Thin-Layer Chromatography

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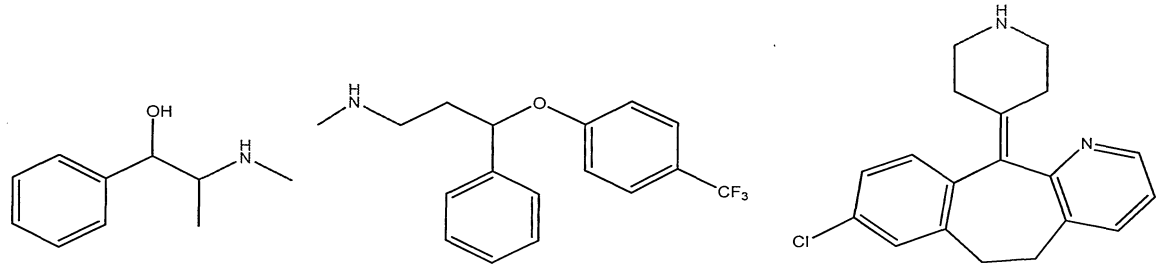
Abstract

Amine bond formation is a major topic in organic chemistry and is widely applied to the formation of medicinal compounds. Current studies have analyzed the benefits of microwave irradiation and solid supported reagents in order to improve reaction conditions and both synthetic and environmental costs. In the synthesis of amines, we investigate the combined use of microwave irradiation and solid supported reagents in the aza-Wittig and reductive amination reaction.

Introduction

Amines are important bioactive compounds that can be found in such drugs as ephedrine **1**, Prozac® **2** (fluoxetine), and Clarinex® **3** (desloratadine) [Figure 1]. One common method of amine synthesis is through nucleophilic substitution. Reagents are limited in this method due to the need of unhindered alkyl halides for the S_N2 mechanism. Further, the alkyl halide is prone to undergo elimination. However, a rough equivalent to such an addition is possible when using acetone as the carbonyl reagent. Another drawback in nucleophilic substitution is the nonbonded electron pair that remains on the nitrogen. This allows the newly formed amine to perform further nucleophilic attacks resulting in a mixture of primary, secondary, and tertiary amines. An alternative method is the reduction of nitro compounds, nitriles, and amides. This involves treating the nitrogen containing compound with a metal hydride reducing agent. The disadvantage to this method is that it often requires strong reducing conditions in order to form the amine. Under such strong conditions it is possible for the reducing agent to react with other functional groups that may be present within the compound.



Ephedrine
1

Fluoxetine
2

Desloratadine
3

Figure 1: Drugs containing secondary amines (red)

Previous work has shown an alternative approach to try to get around problems in the formation of secondary and tertiary amines. This involves the formation of carbon to

nitrogen double bonds (imines) that can be reduced into amines[1] – a process called reductive amination. Typical reductive amination requires acidic conditions in order to synthesize the imine precursor. The nitrogen compound **5** will attack the carbonyl carbon **4** which will allow the acid to protonate the newly formed alcohol **7**. The imine is then formed upon the loss of water **10** [Figure 2].

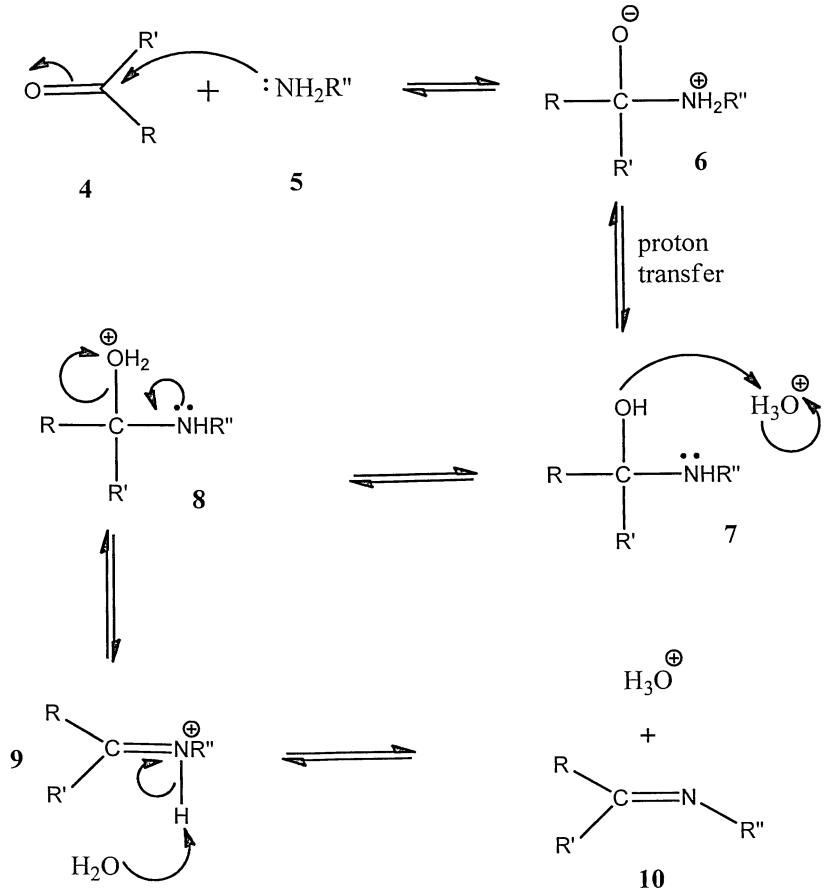


Figure 2: Formation of imine via reductive amination.

However, another method used to form imines employs the use of a Staudinger reaction followed by an aza-Wittig reaction. The Staudinger mechanism calls for a nucleophilic attack by phosphine **11** on the electrophilic azide **12** to synthesize phosphazene **15** after a series of rearrangements [Figure 3].

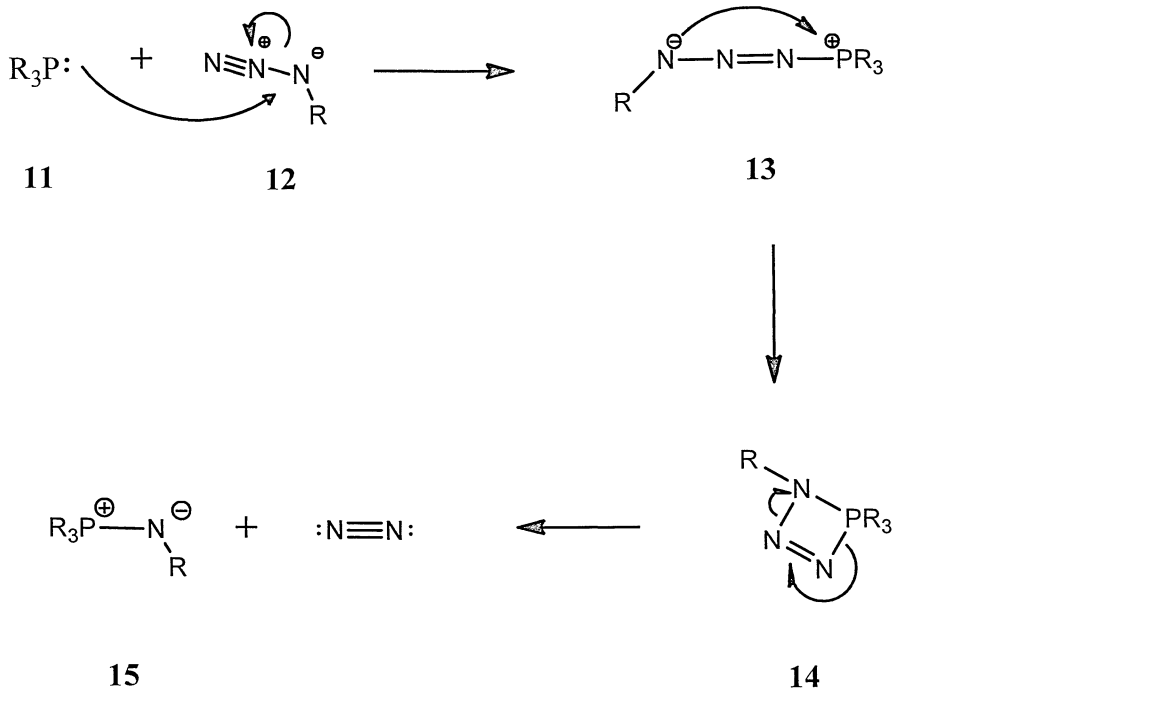


Figure 3: Staudinger Reaction Scheme

The aza-Wittig reaction has been shown to be an effective method for the production of imines, and involves the reaction of phosphazene **16** and either a ketone or aldehyde **17** [Figure 4]. The resulting imine **18** can be reduced to obtain secondary amines **19**. Note this method does not require acidic conditions to form the imine.

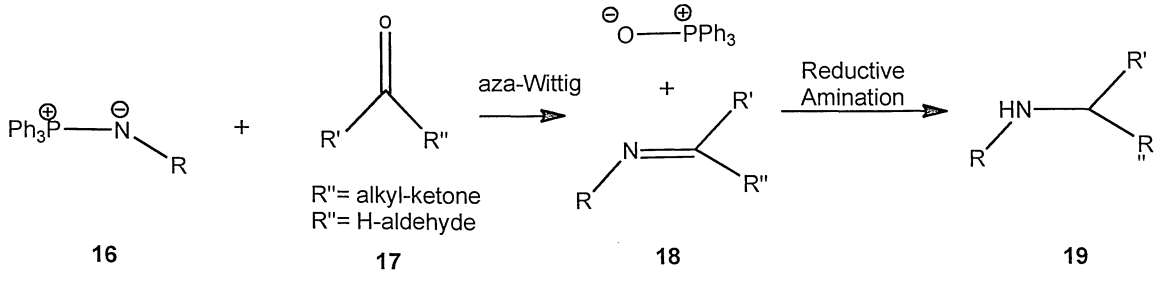


Figure 4: One pot aza-Wittig and reductive amination reaction.

Development of this method was conducted by Hemming and co-workers using polymer supported reagents.[2] Their procedure focused on the combination of azide and aldehyde starting materials to obtain secondary and primary amines. Hemming ran sequential Staudinger, aza-Wittig, and reductive amination reactions in a one pot synthesis. Hemming obtained his product by using conventional heating and running the reaction sequence in the solution phase as shown in Figure 4. Once confirmed, the reaction sequence was transferred to solid phase which facilitated product isolation and purification (to be explained later). Using a solid supported phosphine reagent in the Staudinger reaction created a solid supported phosphazene that could still react with the ketone in the aza-Wittig reaction. The study proved very effective at obtaining high percentage yields of secondary amines. The reaction of starting materials benzaldehyde and benzyl azide showed comparable amine production from a 97% yield in the solution phase up to >99% yield for the polymer phase.[2] Hemming's solution phase procedure required the following: a triphenylphosphine resin, a 2-3 hour (room temperature) stir of the Staudinger reaction in THF followed by a 15 minute reflux, and a 3 hour reflux of the aza-Wittig reaction. The polymer supported procedure included: a polystyrene supported triphenylphosphine, a 2-3 hour (room temperature) shake of the Staudinger reaction, and a 3 hour reflux of the aza-Wittig reaction.[2]

A similar approach was used in this study where we attempted to determine the affect of microwave heating as opposed to conventional heating on the rate of both the aza-Wittig and reductive amination reactions using the solid supported reagents. The use of microwave radiation has been known to improve upon the rate as well as overall percent yield of several organic reactions.[3] Similar to Hemming, our method was

envisioned to utilize a one pot, polymer supported synthesis. We conducted research on two phases of the one pot reaction in order to determine overall optimum conditions for amine production. The first sequence consisted of the Staudinger and subsequent aza-Wittig reactions. The Staudinger reaction between benzyl azide **20** and solid supported triphenylphosphine **21** [Figure 5] was expected to form phosphazene **22** at room temperature based on the previous Staudinger reaction scheme [Figure 3]. The Staudinger reaction would be followed by a microwave-aza-Wittig reaction with the addition of an aldehyde or ketone **23.**

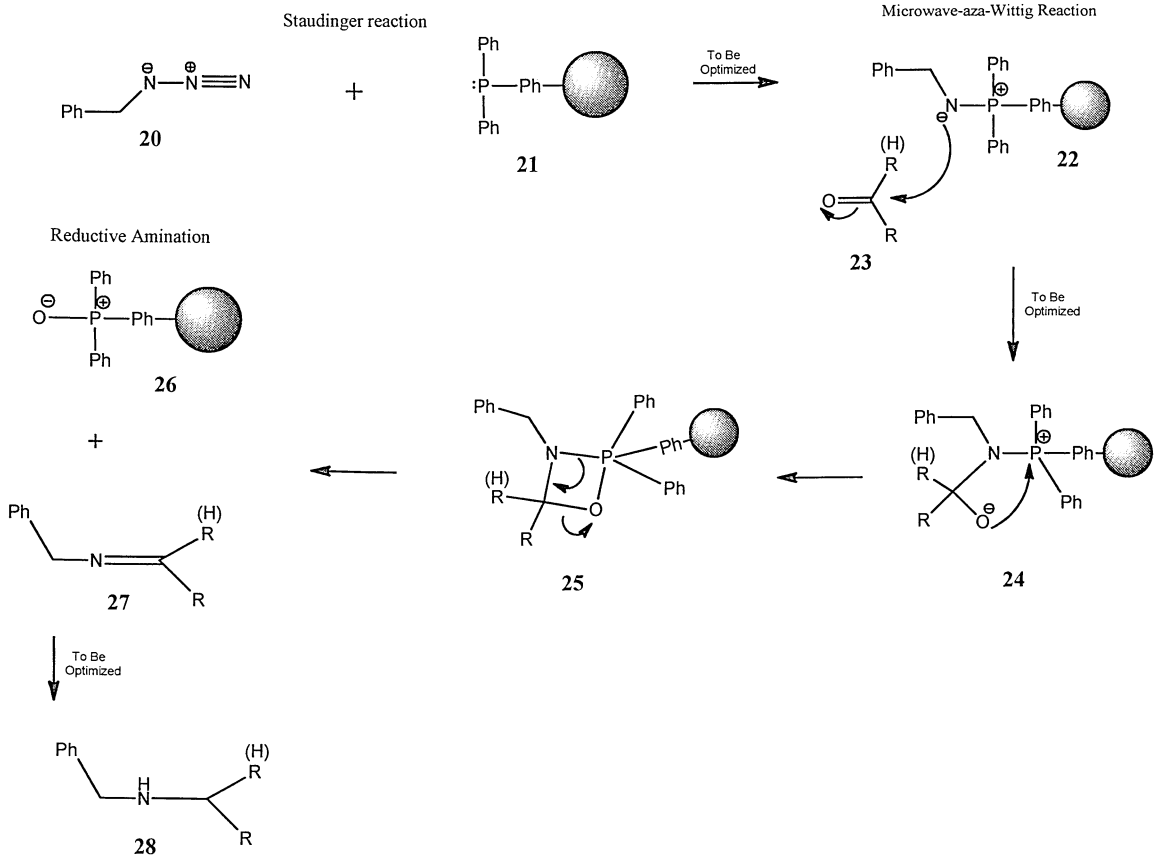


Figure 5: Proposed Reaction Sequence.

The aza-Wittig reaction is a well known method for creating carbon to nitrogen double bonds (imines).[1] The phosphazene **22** serves as the Wittig reagent due to its ylide nature. This allows the negatively charged nitrogen to attack the electrophilic carbonyl carbon in the ketone or aldehyde **23**. This attack creates a betaine structure containing a negative charged oxygen atom and a positively charge phosphorous atom. The negatively charged oxygen will react with the positively charged phosphorus atom **24**. This interaction leads to the formation of a four membered ring containing a strong oxygen to phosphorus bond—oxaazaphosphetidine **25**. This bond creates the driving force for the aza-Wittig reaction. The breakdown of the four membered ring leads to the formation of the imine **27**.[1] Finally, reductive amination, utilizing a solid supported reducing agent would be attempted to produce our intended amine product **28**.

Solid supported reagents can ease purification of a product and reduce the amount of solvent needed to carry out the reaction. Consequently both the economic and environmental cost for performing the reaction could be minimized. Triphenylphosphine in solution phase produces triphenylphosphine oxide byproduct that is a notoriously hard impurity to remove. Utilizing a solid phase support—such as in the work of Hemming—can be expected to produce a resin bound triphenylphosphine oxide **26** side product that could be easily removed from the product by filtration.[2] Thus, by using the polymer supported method it would not require as much time and solvent consuming techniques for product purification.

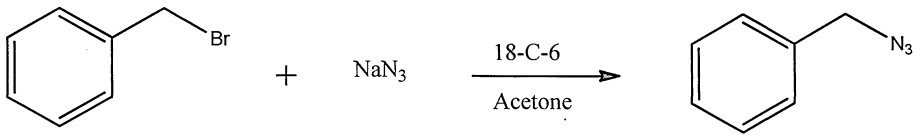
Microwave heating can prove more efficient than conventional heating because it utilizes dielectric polarization, a process that strikes molecules with radiation causing them to align with an applied magnetic field. Similarities in molecular rotational

frequency and microwave radiation frequency will cause molecules to continually attempt to realign with the changing field. Consequently, the molecules will absorb electromagnetic energy that can be transformed into heat energy to drive the reaction.[3] Further, using a conventional heating method can prove wasteful due to the dispersion of heat due to a reflux setup (heating mantle, glassware, etc.). Additional benefits of microwaves come from an increased systematic control in such factors as reaction temperature and pressure. These benefits allow microwaves to heat solvents beyond their boiling points and consequently improve reaction rates.[4] Applying this knowledge, we have investigated various conditions to improve upon Hemming and coworkers reaction rates and reduce the amount of time needed for each reaction.

Results & Discussion

The S_N2 reaction of benzyl bromide **29** and sodium azide **30** in a solution of acetone and 18-crown-6 produced the benzyl azide reagent **20** needed for the Staudinger reaction [Figure 6]. The ^1H NMR (Spectrum 1) data showed a singlet peak at 4.32 ppm with an integration of two hydrogens. There was also a multiplet peak at approximately 7.35 ppm with an integration of five hydrogens. This signified the five hydrogens bonded to the sp^2 carbons of the aromatic ring. The infrared spectroscopy data (Spectrum 2) contained the following peaks: strong absorbance at 2100 cm^{-1}, absorbance at 1700 cm^{-1}, and absorbance spanning 2850 cm^{-1} – 3130 cm^{-1}. The strong absorption at 2100 cm^{-1} is common of the azide functional group. The 1700 cm^{-1} absorbance is expected for aromatic groups and is therefore contributed by the benzene ring. The absorbance range of 2850 cm^{-1} – 3130 cm^{-1} contains the sp^3 and sp^2 carbon atoms bonded to hydrogen. With this information, we can conclude that expectations were met for the benzyl azide

reaction. The final product was isolated with a 90.12% yield, which shows that the azide (nucleophile) and the bromine atom (leaving group) are able to react effectively under simple S_N2 conditions.

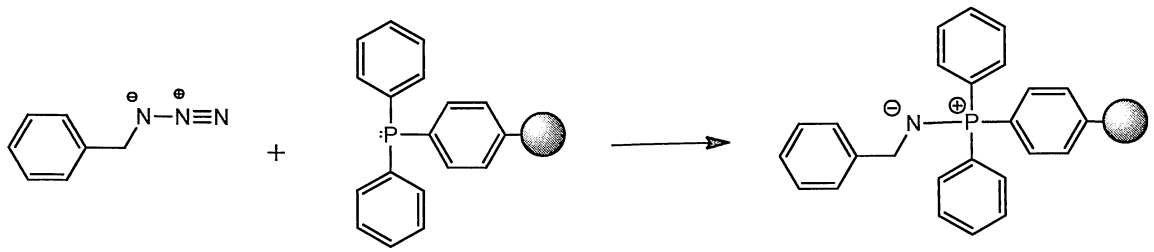


29 **30** **20**

Figure 6: Formation of Benzyl Azide

The ^1H NMR and IR spectra agree with literature values for benzyl azide.[5] After formation of the benzyl azide, the next step focused on optimizing the Staudinger reaction conditions.

The Staudinger reaction was performed according to a similar literature procedure.[5] We utilized a resin bound triphenylphosphine **21** to react with benzyl azide **20** in order to form phosphazene **22** [Figure 7].



20 **21** **22**

Figure 7: Staudinger Reaction

We used thin-layer chromatography (TLC) to first monitor the reaction of the benzyl azide with the triphenylphosphine resin. We soaked the resin overnight in 5mL of THF. The next day benzyl azide was added to the solution in an equimolar amount as the

triphenylphosphine based on the loading of the resin. The reaction was stirred and TLC samples were taken in one minute intervals for the first five minutes and then on five and ten minute intervals after that. The phosphine reagent immobilized on the resin would cause the benzyl azide to disappear from the TLC as it reacts with the resin. The results showed that the benzyl azide did not disappear from TLC in the 30 minute time interval which indicated that the reaction did not go to completion.

We next used infrared spectroscopy (IR) to achieve better monitoring of the Staudinger reaction. The IR spectra (Spectrum 3) provided a qualitative way to identify the functional groups present in the reaction solution. We could better monitor the completion of the reaction by monitoring the absorption peak at 2100 cm^{-1} and seeing it disappear over time as the benzyl azide reagent reacts with the resin. Samples of the Staudinger reaction were removed for IR analysis in 10 minute intervals for 30 minutes. Given that the azide functional group is notorious for producing a strong absorbance at 2100 cm^{-1}, we monitored the loss of the peak as the reaction proceeded. The IR showed that the azide functional group of the benzyl azide disappears significantly in the 30 minute interval. Thus, we determined the Staudinger reaction stir time—30 minutes—was sufficient according to IR spectroscopy.

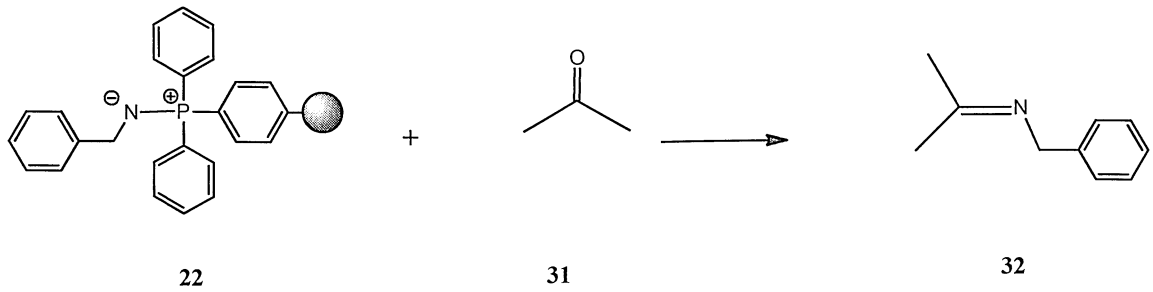
Reactions of **22** with benzaldehyde in a 1:1 mole ratio failed to produce the desired imine product in both a THF and toluene solvent. Both the reaction time and temperature were increased in order to drive the reaction [Table 1]. The resulting ^{1}H NMR data—however—still provided no evidence of imine formation.

Solvent	[Benzyl Azide] : [Triphenylphosphine]	Time	Temp
THF	1 mol: 1 mol	30 minutes	65°C
Toluene	1 mol: 1 mol	30 minutes	100°C
	1 mol: 1 mol	60 minutes	100°C

Table 1. Reaction conditions for the benzaldehyde trials.

In an attempt to change the reaction conditions to more greatly favor imine formation we attempted the reaction in pure acetone solvent and monitored by GC-MS.

The acetone **31** provides both a good microwave solvent and a ketone that could possibly react in the aza-Wittig reaction to form the imine **32**. [Figure 8].



22 **31** **32**

Figure 8: aza-Wittig Reaction

The first acetone trial utilized the previously developed conditions: 30 minute Staudinger reaction stir (room temperature), followed by 60 minute microwave-aza-Wittig, and a 60 minute microwave reductive amination in an equivalent amount of sodium cyanoborohydride and 2.5 mL of methanol. The only difference came in the use of acetone which would serve not only as a solvent but as a ketone reagent in the aza-Wittig. We used a total of 2.5 mL of acetone for the solvent and reagent. Using the acetone as a combined solvent and reagent essentially creates a very concentrated amount of reagent thereby giving the phosphazene **22** a greater chance of coming into contact

with the carbonyl of the acetone **31**. As a result, the reaction could be pushed further toward imine formation

The GC-MS for the 60 minute microwave-aza-Wittig (Spectrum 4) contained a *m/z* peak of 146 at 7.854 minutes, which represents an M-1 peak for the imine **32**. The same solution contained a *m/z* peak of 133 at 6.752 minutes, which matches the mass of the benzyl azide **20** (for the 1st trial the microwave temperature was 100 °C for about 40 minutes then changed to 60°C for approximately the last 20 minutes of the microwave aza-Wittig). Further, the GC-MS following reductive amination (Spectrum 5) also detects the *m/z* = 133 azide peak at minute 6.751 and the *m/z* = 146 (M-1) peak of the imine at minute 7.854. It does not—however—contain a *m/z* peak of 149 for the amine.

This data provided much more insight into the progress of the reaction. It showed the presence of azide in the reaction solution which—until GC-MS—was undetected. This suggested that the Staudinger reaction may not be reaching completion. Thus, further adjustments need to be made to the method in order to insure that the Staudinger reaction reaches completion. This could possibly mean a longer stir time or changing the ratio of reagents. The microwave-aza-Wittig reaction showed promise, though it did not reach completion. The *m/z* = 146 peak informed us that the reaction was producing imine like we intended. The reaction appeared slow and the phosphazene was likely bound to the resin, which would explain why it was undetected by GC-MS. On the other hand, the microwave reductive amination did not work at all. This prompted us to focus on developing more favorable imine formation conditions. The research shifted focus to the partially complete Staudinger and aza-Wittig reactions and adjusting conditions [Table 2] of the acetone system.

Staudinger and aza-Wittig Conditions					
	Reagent	benzyl azide: triphenylphosphine	Staudinger Stir	Δ-aza-Wittig	Temperature (°C)
Reaction 1	excess acetone	1 mol : 1 mol	30 min	1 hr	100 down to 60 (last 20 minutes)
Reaction 2	excess acetone	1 mol : 1.2 mol	60 min	1 hr	60
Reaction 3	acetone (10:1 mole ratio) *	1 mol : 1.2 mol	60 min	1 hr	60

Table 2. Staudinger and aza-Wittig reaction conditions for the acetone trials.

* THF used as solvent.

A repeated reaction through to the aza-Wittig step was conducted with the following changes: Staudinger stir time doubled to one hour, ratio of triphenylphosphine to benzyl azide changed to 1.2 mole : 1 mole, and microwave temperature dropped to 60 °C instead of 100 °C. According to previous TLC and IR data it seemed a 30 minute Staudinger stir time was sufficient. However, the addition of GC-MS data indicated this was not correct and prompted the increase to a 60 minute stir time and the reagent ratio change from 1:1. This would favor the completion of the Staudinger reaction to help maximize imine formation. The reaction temperature was changed to 60 °C due to the lower boiling point of the acetone solvent.

Similar to the previous trial, the GC-MS data for the end of the one hour microwave aza-Wittig reaction showed the imine *m/z* peak of 146.0 at minute 7.810 (Spectrum 6) and the azide *m/z* peak of 133 at minute 6.754. These results suggested the issue we had with the completion of the Staudinger reaction is still not solved. Therefore, we decided to take it one step further by testing the acetone reagent in a THF solvent. Using the THF solvent has the potential benefit of more effectively penetrating the polystyrene of the solid supported triphenylphosphine. Formation of the imine indicated

that the aza-Wittig reaction was still taking place, although it was unable to go to completion as well.

We conducted another reaction to the microwave-aza-Wittig. All conditions were kept the same except the 2.5 mL of acetone was switched to 2.5 mL of THF. At the end of the Staudinger reaction we added 10 equivalents of acetone to benzyl azide (1.0 mmol acetone: 0.1 mmol benzyl azide). The THF solvent will change the reaction by allowing the azide reagent to react fully with the triphenylphosphine that was also contained within the polystyrene beads and not just on the resin surface. This further insures the completion of the Staudinger reaction.

Once again, the results were similar. The GC-MS data (Spectrum 7) shows the azide *m/z* 133 (M-1) peak at minute 6.757 for the end of the one hour microwave-aza-Wittig reaction. There is also the *m/z* 146 (M-1) peak of the imine at minute 7.824. Neither the Staudinger nor the microwave-aza-Wittig are reaching completion. For this trial we also saw a drop off in the rate of imine production for the aza-Wittig. This is likely due to switching to the THF solvent which causes the loss of the high concentration of acetone reagent. Thus, more adjustments need to be done in order to achieve the completion of the Staudinger and microwave-aza-Wittig reaction. We are currently working to find optimal conditions and monitoring the microwave reaction time to determine any benefit in microwave radiation compared to conventional heating.

The microwave reductive amination reaction was the final step in the sequential one pot synthesis. It required adding the final aza-Wittig reaction solution to a new solution of methanol and sodium cyanoborohydride. The reaction would use the microwave for an additional hour in order to form the amine. Using TLC conditions of

5% methanol in methylene chloride lead us to believe the reaction was forming an amine product after the reductive amination. However, with more insight from the GC-MS data it seems that we are seeing unidentified side product and not the amine as of yet. The microwave reductive amination step is insufficient at the moment, but will be worth revisiting after optimizing conditions for the previous reactions (Staudinger and microwave aza-Wittig).

Conclusion

At this point the method is insufficient in terms of amine formation. The reductive amination reaction did not work under our current conditions. Based on the spectral data we can conclude that the benzyl azide, Staudinger, and aza-Wittig reactions are producing our intended products. We were able to isolate benzyl azide in significant yield (90.12%) showing that conditions for this reaction are sufficient for the method. However, the Staudinger and aza-Wittig reactions need to be optimized. This can be achieved with further investigation into alternative reaction conditions (reaction time, reagents and their ratios, solvents, etc.). As soon as these reactions are optimized we will be able to investigate any improvements in microwave irradiation as opposed to conventional heating.

General Methods

All supplies were provided by the Butler University Chemistry Department. Each reagent and solvent was used without additional purification of their original purchase from Sigma-Aldrich or Acros. The resin was purchased from Nova Biochem. The infrared spectroscopy data was obtained using Nicolet Avatar 300-FT-IR. The aza-Wittig

and reductive amination reactions were heated using a Discover® CEM Microwave. All TLC plates were made of Polygram® silica gel, made by Macherey-Nagel.

Experimental Methods

Preparation of benzyl azide 20: 1.1877 mL of benzylbromide (10 mmol) and 1.6250 g of sodium azide (25 mmol) were added to a solution of 0.2643 g of 18-crown-6 (1 mmol) and acetone (10 mL) solvent. The solution was stirred at room temperature for 2.5 hours. The reaction was diluted with water (5 mL) and then extracted three times with ether (5 mL). After the extraction, the reaction was dried with magnesium sulfate and filtered using suction filtration. The solvent was removed under reduced pressure using rotary evaporation. The final product was a yellow, oily liquid **20**.

Data: The reaction produced a 90.12% yield. ^{1}H NMR: 4.32 (s, 2H, N_3-CH_2-Ph), ~7.35 (m, 5H, Csp^2-H of the phenyl); IR: strong 2100 cm^{-1} (azide), 1700 cm^{-1} (aromatic), 2850 – 3130 (Csp^3-H and Csp^2-H of aromatic)

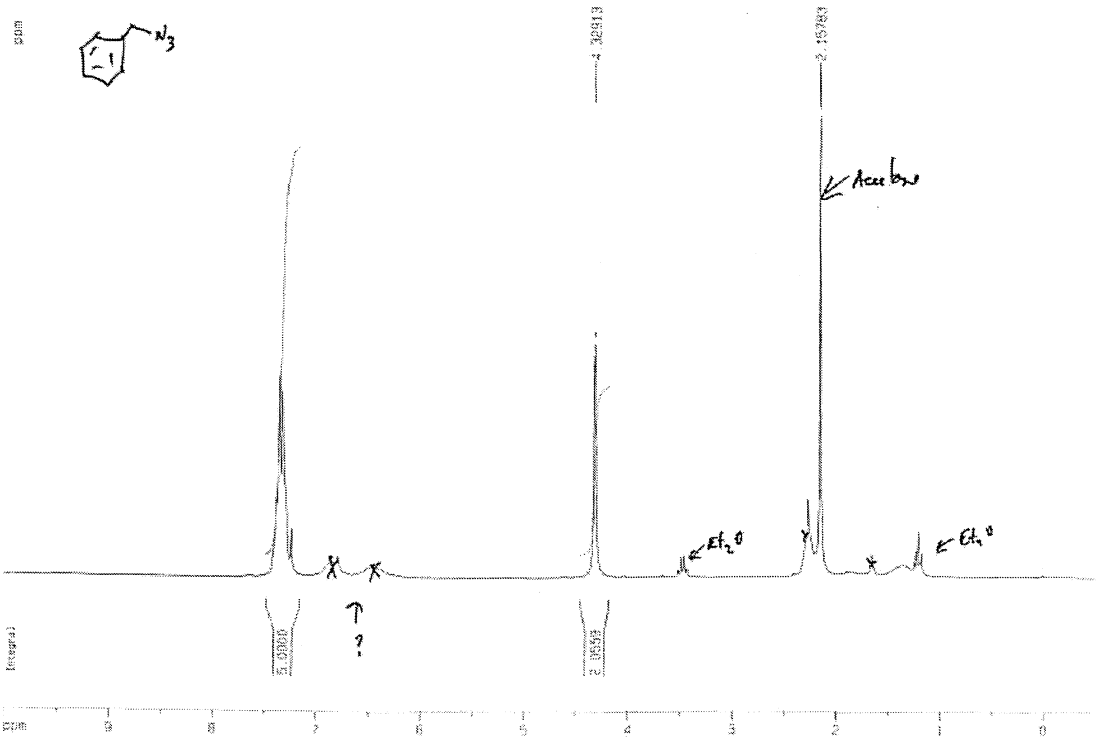
Optimization of Staudinger Reaction: 0.110 g of triphenylphosphine resin (0.1 mmol) was added to solvent and washed for 5 minutes. We initially used THF (5 mL) solvent. Then we dropped the volume in half to THF (2.5 mL). Finally we ran the reaction with toluene solvent (2.5 mL). Benzyl azide (0.1 mmol) was added to the solution by measuring 0.0133 g of the liquid because the volume was so small. The reaction stirred for 60 minutes at room temperature. Samples were taken for TLC analysis in 1 minute intervals for 5 minutes and then 5 minute intervals there after. Elution solvents of 9:1 and 1:1 (hexane:ethyl acetate) were stained in PMA and ninhydrin in order to monitor the reaction.

Optimization of aza-Wittig Reaction: For the benzaldehyde trials: 0.0114 mL of benzaldehyde (0.1 mmol) was added to the reaction solution upon completion of the various Staudinger reaction times. The reaction tube was taken to the microwave to react for one hour at the temperature required of the solvent (60 °C or 100 °C). Samples were taken for TLC before and after the reaction completion.

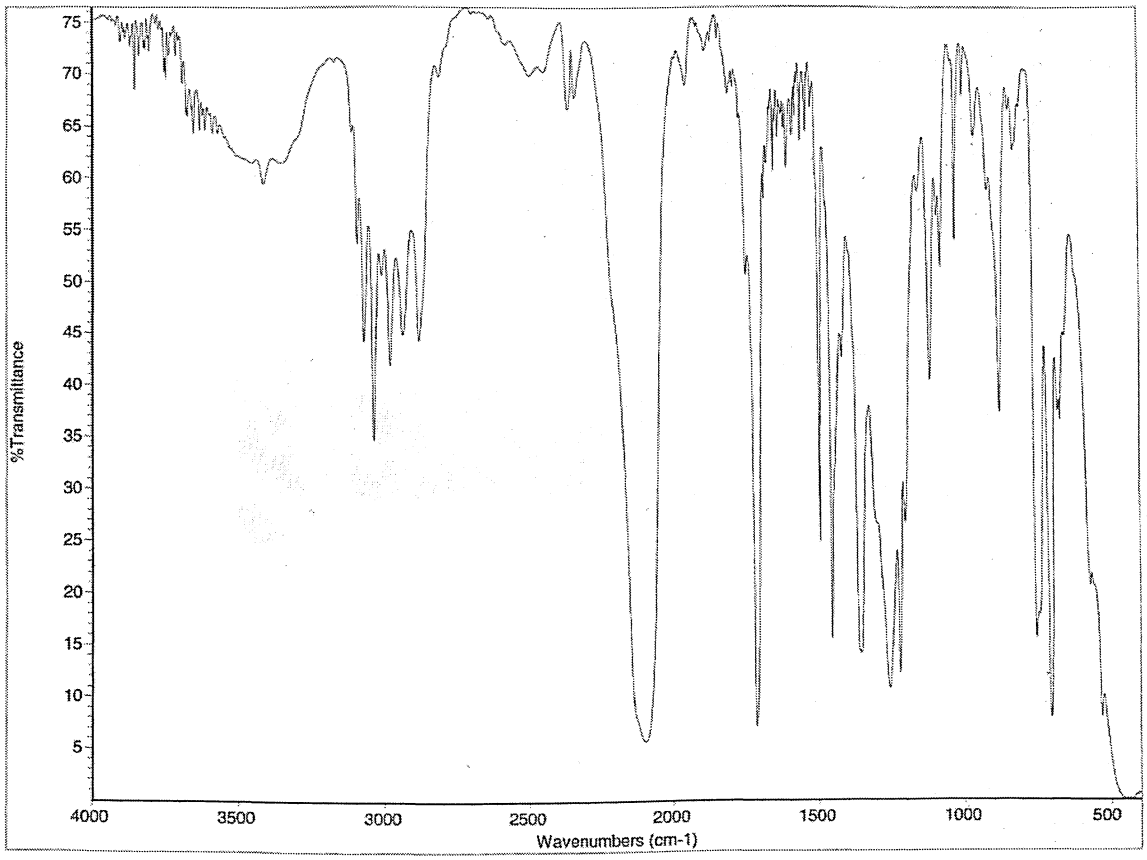
For the acetone trials: the reaction of the acetone solvent and reagent combination was moved to the microwave—after Staudinger—to react for one hour at 60° C. When running the reaction of acetone in a THF solvent: 0.0734 mL of acetone (1 mmol) was added to the reaction solution and then moved to the microwave to react at 60 °C for one hour. The reaction samples were prepared for GC-MS in the following manner: at the necessary time two drops of the reaction solution were added to a small, plastic vial. The drops were then diluted with methylene chloride and ran on the GC-MS instrument.

Reductive amination: At the end of the aza-Wittig reaction the reaction solution was moved to a new reaction tube containing 0.02558 g of sodium cyanoborohydride (0.1 mmol) and methanol (2.5 mL). The reductive amination tube was microwaved for one hour at the same temperature used for the aza-Wittig. The TLC was worked up in an elution solution of 5% methanol in methylene chloride and stained with ninhydrin.

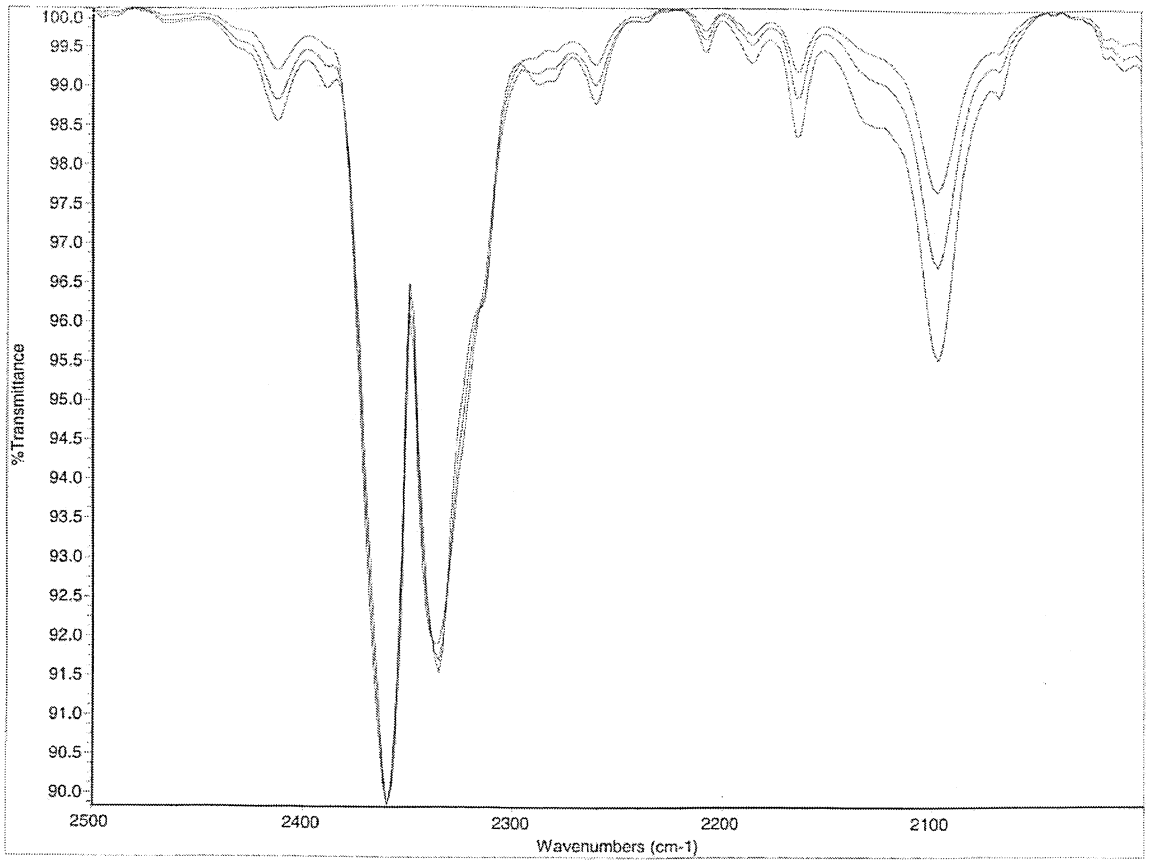
Appendix A: Spectral Data



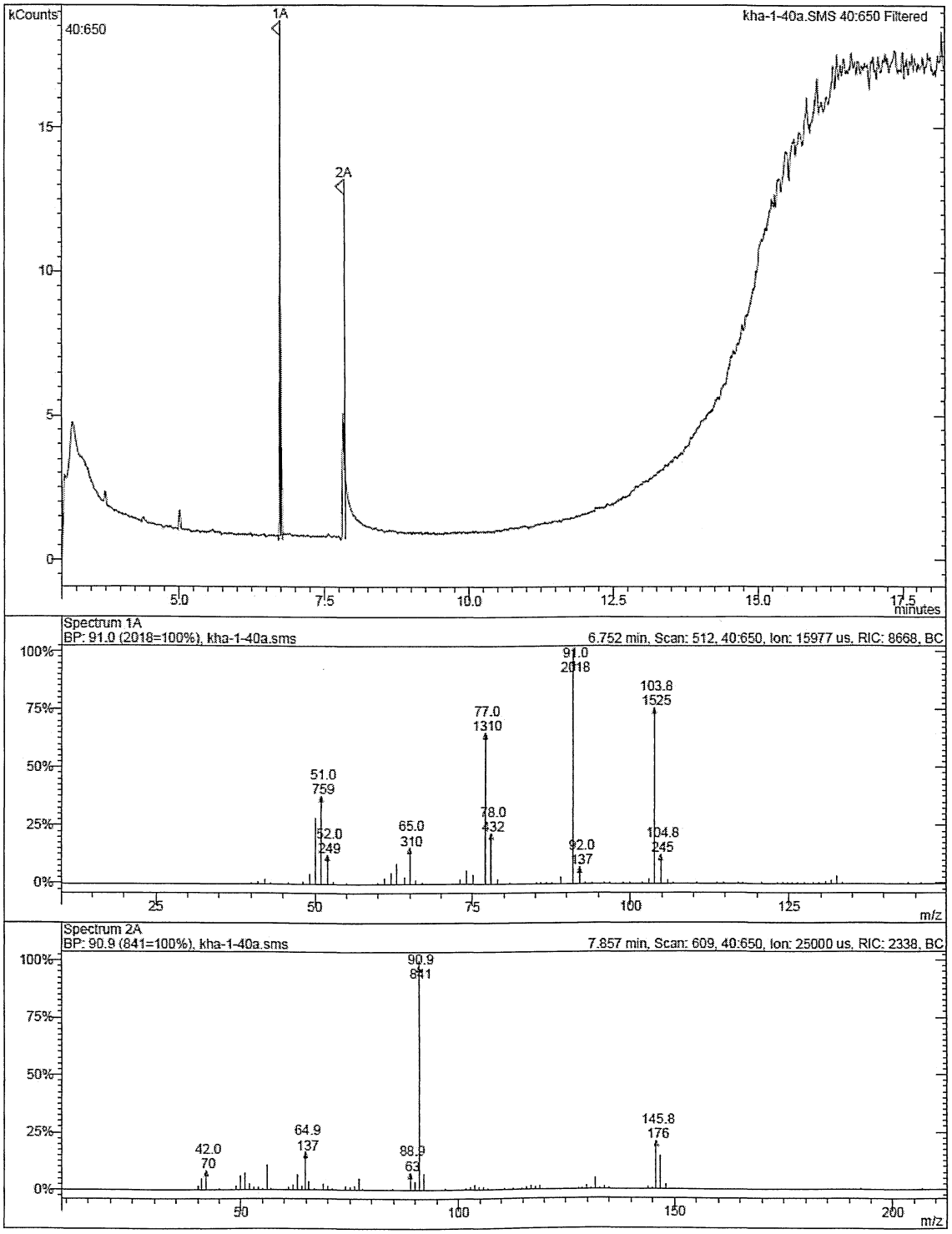
Spectrum 1. ^{1}H NMR of benzyl azide.



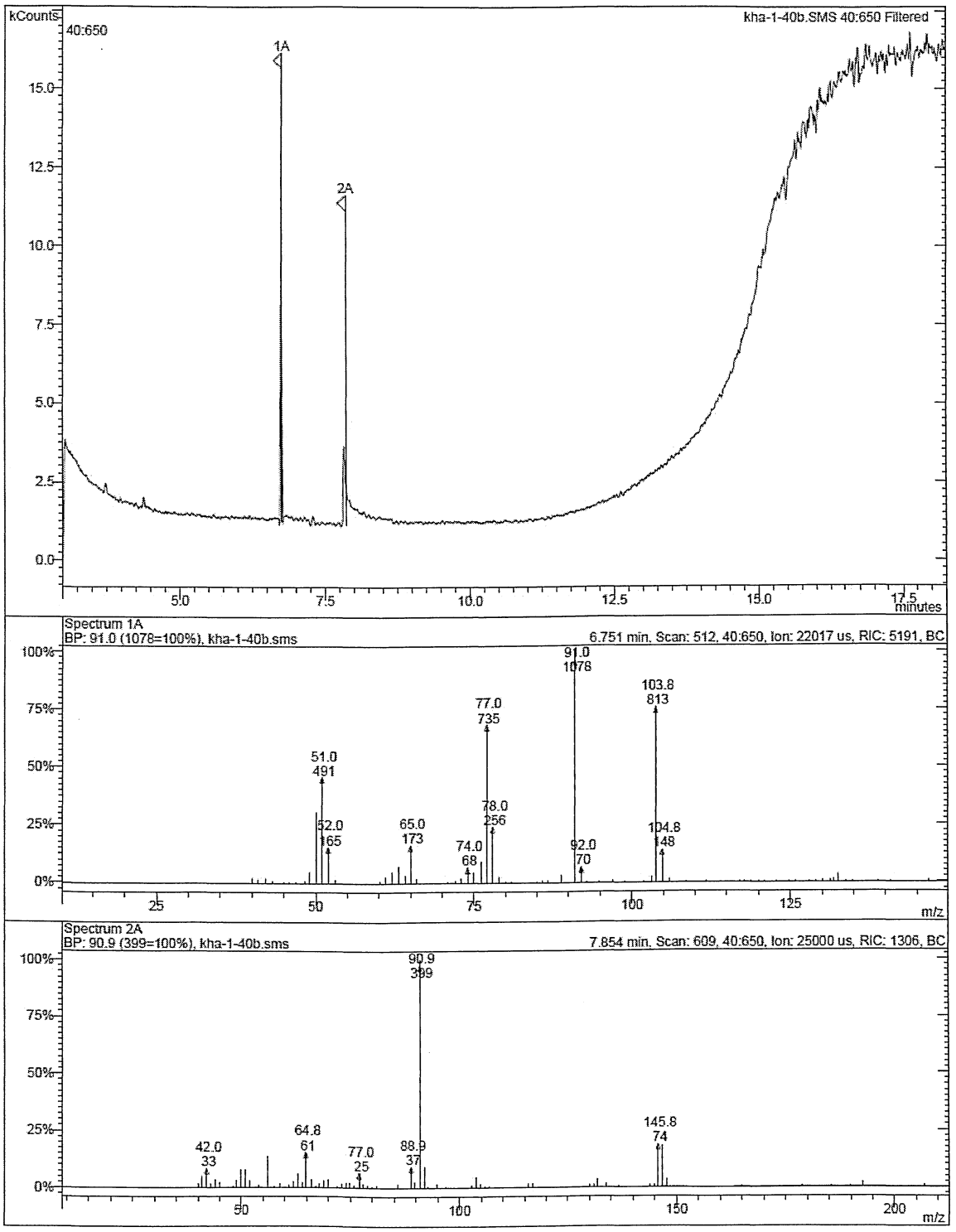
Spectrum 2. IR of benzyl azide.



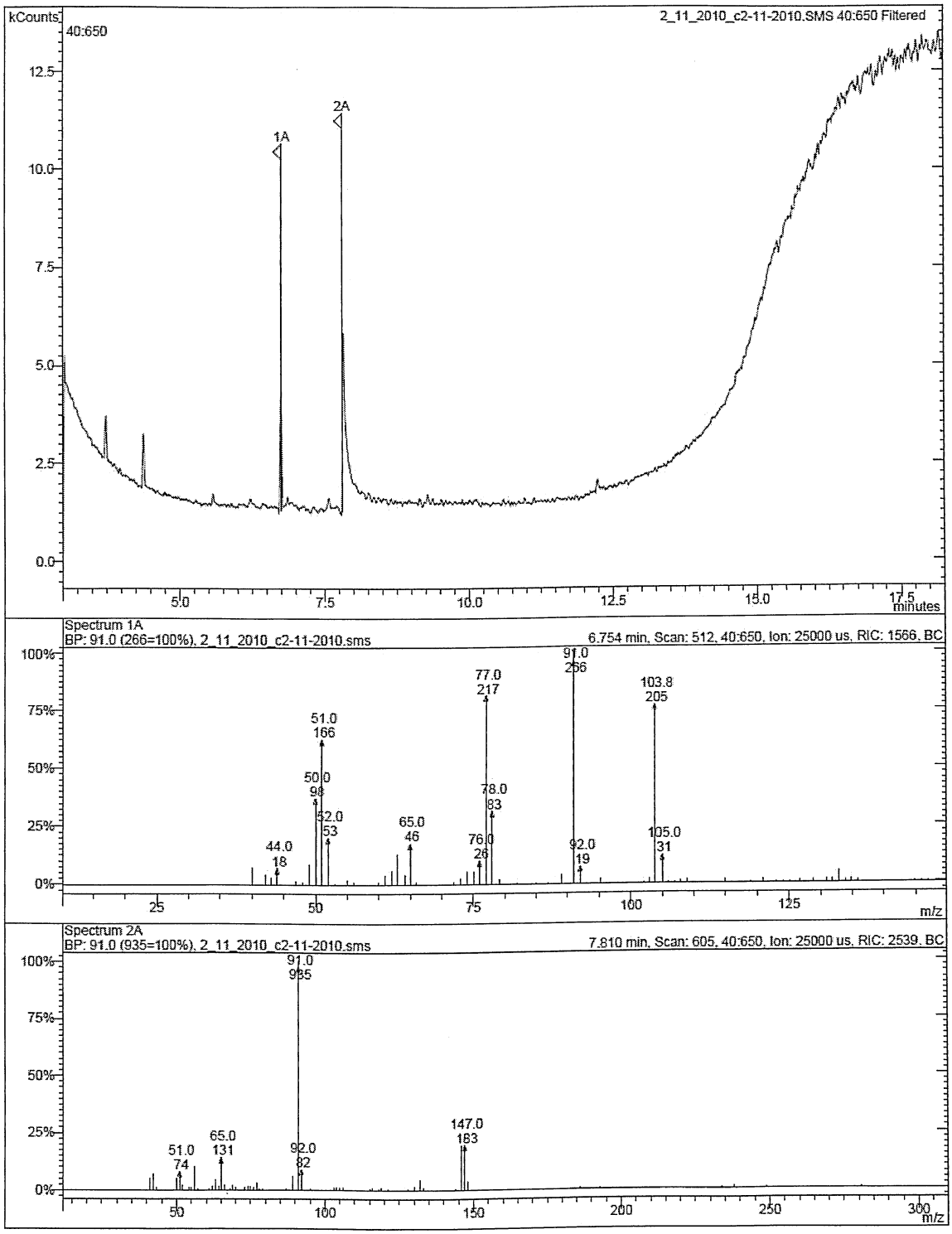
Spectrum 3. IR of Staudinger reaction completion.



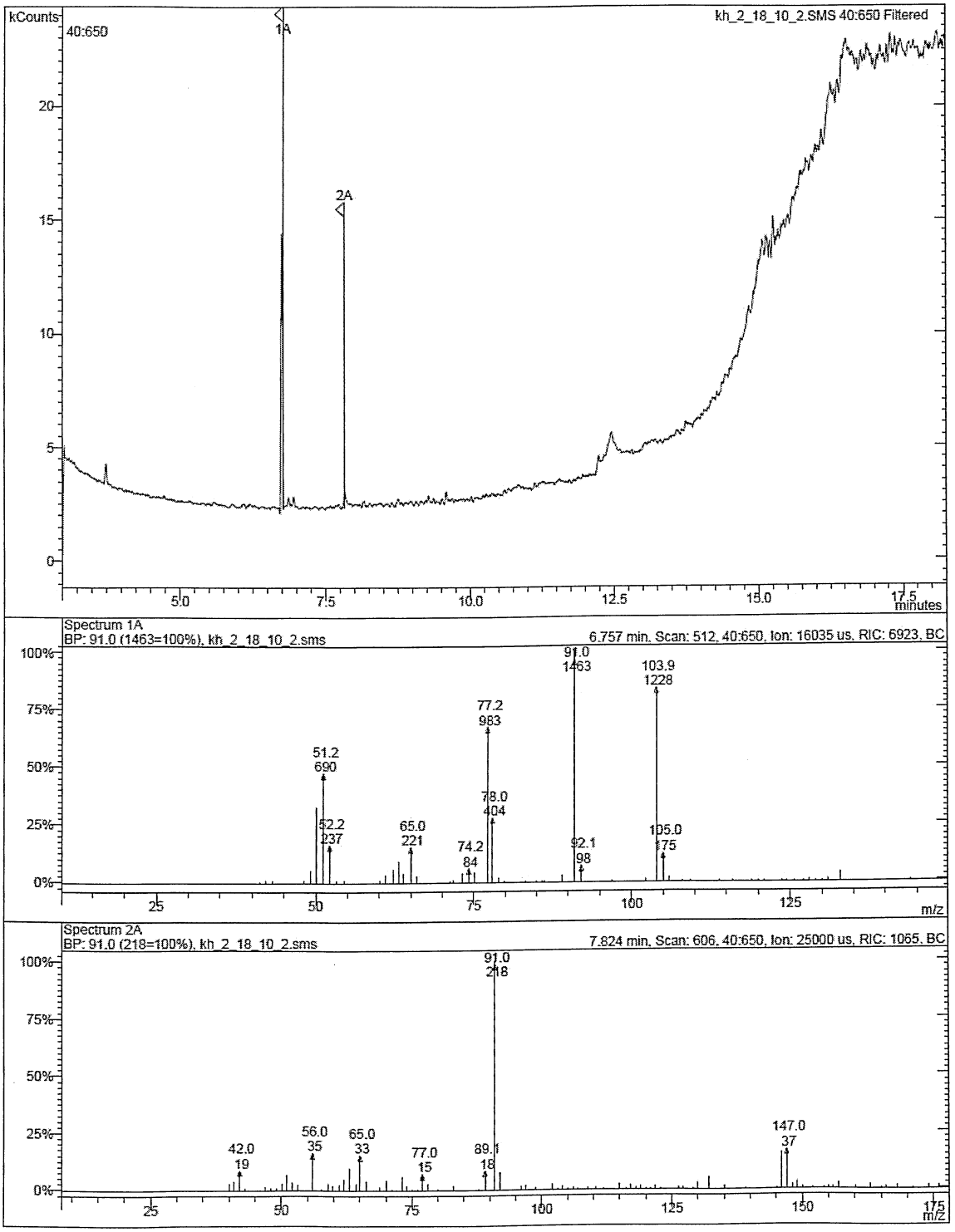
Spectrum 4. GC-MS of microwave-aza-Wittig (acetone trial 1)



Spectrum 5. GC-MS of reductive amination (acetone trial 1)



Spectrum 6. GC-MS of microwave-aza-Wittig (acetone trial 2)



Spectrum 7. GC-MS of microwave-aza-Wittig (acetone trial 3)

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